UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,333	11/14/2001	Larry Wayne Oberley	875.042US1	5690

21186 7590 09/06/2007

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
09/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/993,333	OBERLEY ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-8,11-15,18-21 and 23-31* is/are pending in the application.

4a) Of the above claim(s) *5,23-26,28 and 29* is/are withdrawn from consideration.

5)☒ Claim(s) *20 and 21* is/are allowed.

6)☒ Claim(s) *2, 3, 6-8, 11-15, 18, 19, 27, and 30* is/are rejected.

7)☒ Claim(s) *31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2001 and 14 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group I, claims 2, 3, 6-8, 11-15, 18-21, 27, 30 and 31, in the reply filed on 6/14/07 is acknowledged. The traversal is on the ground(s) that a search has been done for methods not limited to a particular cancer and thus there is no serious burden on the examiner. Although the claims reciting specific cancers (claims 27-29) are dependent on a generic claim that is not limited to one specific type of cancer (claim 8), a search for any of the specific methods directed to treating a specific cancer would require a separate and distinct search and corresponding examination.

As explained in the restriction requirement mailed on 5/14/07, claim 8 links the inventions of groups I-III and therefore the restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 8. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5, 23-26, 28 and 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/14/07.

Applicant's arguments and/or amendments filed 2/23/07, with respect to the rejection(s) of the claim(s) under 35 U.S.C. 112, 2nd paragraph, as well as claim 22 under 35 U.S.C. 102(b), have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made.

Response to Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 11-15, 18, 19 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of **breast cancer** using the claimed antisense oligonucleotides via **intratumoral injection**, does not reasonably provide enablement for treatment of any tumor using the claimed antisense oligonucleotides via any method of delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

practice the invention commensurate in scope with these claims, as explained in the office action mailed on 8/24/06.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

It is noted that the instant rejection is maintained with respect to the breadth of the claims regarding recitation of treating any tumor type. Additionally, applicant is not enabled for a method of treating any tumor in a mammal (including breast cancer tumors) via any mode of administration, as delivery is known in the art to be a source of antisense oligonucleotide unpredictability.

Therefore, applicant is enabled for a method of treating a **breast cancer** tumor in a mammal comprising administering via **intratumoral injection** to a mammal having the tumor a therapeutically effective amount of the claimed antisense nucleic acids.

Although applicant asserts that the claims are supported by a number of working examples, the only *in vivo* working example disclosed in the instant specification is that

of treating breast cancer tumors with the instant oligonucleotide via xenografts delivered via intratumoral injection, which is not commensurate in scope with the instantly recited claims directed to treating any tumor type and/or via any mode of administration.

The teachings of the specification regarding treating other tumor types, such as melanoma and glioma are *in vitro* examples and are therefore not commensurate in scope with the instant claims which recite "a method of treating a tumor in a mammal".

The specification describes prophetic methods of treatment using antisense oligos targeted to human manganese superoxide dismutase, and further exemplifies method of using the claimed composition to inhibit the expression of human manganese superoxide dismutase in a mouse xenograft injected with MCF-7 cells, which had the effect of inhibiting tumor growth in said model.

Applicant asserts that Church et al. cannot indicate unpredictability in practicing the instant invention because the tumor cells of Church et al. have little steady-state MnSOD expression. Contrary to applicant's assertion, the method and molecules utilized by Church et al. do not need to be identical to the instant method and molecules. Church et al. teach that increasing manganese superoxide dismutase expression actually suppresses the malignant phenotype of human melanoma cells. This runs contrary to the underlying principle of the instantly claimed invention, whereby inhibition of the same target is claimed to suppress the malignant phenotype in humans. Regardless of the specific molecules used or the steady-state level of MnSOD expression, Church et al. increased the expression of manganese superoxide dismutase and got a result that is contrary to the instant principle. Accordingly, the

claimed invention cannot work over its entire breadth, since the combination of the specification and the prior art teach suppression of malignancy resulting from both increasing and decreasing the expression of the instantly recited target. Although applicant asserts that the amount of experimentation needed is not undue, the examples in the instant specification regarding tumor types other than breast cancer are *in vitro* and are not necessarily predictable of *in vivo* activity. Church et al. is additional evidence that suggests that inhibition of the identical target would have the opposite effect in at least one other cancer type, further supporting the unpredictability of the instant breadth.

Furthermore, with regards to delivery of the instant antisense oligonucleotide, there is no guidance in the specification as filed that teaches how to deliver the antisense oligonucleotide *in vivo* other than via intratumoral injection, which is not commensurate in scope with the instant claims. The state of the art prior art is such that inhibition of gene expression *in vitro* is routine, but *in vivo* inhibition of gene expression with a resultant therapeutic effect at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in*

vivo (whole organism). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

Jen et al. state (Stem Cells 2000, Vol. 18, p 307-319; see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Crooke, (Antisense Research and Application, Chapter 1, Springer-Verlag, New York. 1998) states on p. 3, paragraph 2, "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies."

Scherer et al., for example, illustrates the state of the art for delivery of nucleic acid molecules *in vivo*. Scherer et al. (Nat. Biotechnol., 2003, 21(12), pages 1457-1465) teach that antisense oligonucleotides (ODNs), ribozymes, DNAzymes and RNA interference (RNAi) each face remarkably similar problems for effective application: efficient delivery, enhanced stability, minimization of off-target effects and identification of sensitive sites in the target RNAs. Scherer et al. teach that these challenges have

been in existence from the first attempts to use antisense research tools, and need to be met before any antisense molecule can become widely accepted.

It is well known that there is a high level of unpredictability in the nucleic acid art for predictable *in vivo* delivery of antisense oligonucleotides with a resultant therapeutic effect. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely a broad method of delivering an antisense oligonucleotide via any means of administration *in vivo* and/or a resultant treatment effect on any tumor type.

It is noted that the disclosure is required to be enabled over the instant scope at the time of filing:

MPEP 2164.01
Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, **when filed**, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention.

Also, MPEP 2164.01(a) (this is good because it cites case law)
A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* whether introduction of the antisense oligonucleotide *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful delivery in order to treat such a broad scope of tumor types. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of

the antisense molecule *in vivo*, delivery of the antisense molecule to the whole organism, and entry of the antisense molecule into the cell *in vivo* with effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

In conclusion, applicant is enabled for a method of treating a **breast cancer** tumor in a mammal comprising administering via **intratumoral injection** to a mammal having the tumor a therapeutically effective amount of the claimed antisense nucleic acids. It is noted that applicant has a claim reciting that the antisense nucleic acid sequence is injected into the tumor (claim 11) and a claim reciting that the tumor is a breast cancer tumor (claim 27), however there are no pending claims that recite these enabled elements together.

Response to Claim Rejections - 35 USC § 102

Claims 2, 3, 6, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Kinscherf et al. (FASEB J. 1998, 12:461-467), as explained in the office action mailed on 8/24/06.

Applicant has cancelled claim 22, thereby obviating the rejection against this claim.

As explained in the office action mailed on 8/24/06, Kinscherf et al. teach an antisense nucleic acid sequence containing phosphorothioate linkages that is 22 nucleotides in length, which is considered to be about 20 nucleotides in length, and is

100% complementary to the start codon of the nucleic acid encoding the human manganese superoxide dismutase.

Applicant asserts that the sequence of Kinscherf et al. is not at least 90%, let alone 100%, complementary to a contiguous portion of a nucleic acid that encodes a human manganese superoxide dismutase, wherein the contiguous portion includes the start codon. Applicant points to Exhibit A that shows an alignment of the human manganese sequence with the Kinscherf et al. sequence.

As instantly recited, the entire oligonucleotide sequence does not need to be at least 90%, or 100% complementary to a contiguous portion of a nucleic acid that encodes a human manganese superoxide dismutase, but rather the oligonucleotide is at least 90%, or 100% complementary to and binds specifically binds to a contiguous portion of a nucleic acid that encodes a human manganese superoxide dismutase, wherein the contiguous portion includes the start codon.

As evidenced by applicant's Exhibit A, the sequence of Kinscherf et al. meets the instant size limitations and is 100% complementary to a contiguous portion of a nucleic acid that encodes a human manganese superoxide dismutase, wherein the contiguous portion includes the start codon. For example, nucleotides "TACAAC" of Kinscherf et al. represent sequences that are 100% complementary to a contiguous portion of the nucleic acid including the start codon. The instant claims do not recite any length limitation of the contiguous sequence.

Therefore, the instant claims are anticipated by Kinscherf et al.

New Objections/Rejections

Claim Objections

Claim 31 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 13 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 13 are directed to the method of claim 8, wherein the "therapeutic agent" is injected into the tumor or further comprises a delivery vehicle, respectively. Claim 8 does not recite a "therapeutic agent" and therefore there is insufficient antecedent basis for this limitation in the claim.

Claim 30 is directed to the oligonucleotide of claim 6, which is 18 to 26 nucleotides in length and is at least 90% identical to SEQ ID NO: 2. However, oligonucleotides within the instant size range that are 23, 24, 25, or 26 nucleotides in length cannot meet the instant claim limitation of being at least 90% identical to SEQ ID NO: 2, which is a 20-mer. For example, even if a 23-mer comprises the 20-mer, it is still only 87% identical to SEQ ID NO: 2 (the maximum potential identity is 20/23). If a 24-

mer comprises the 20-mer, the maximum potential identity is 20/24, which is 83%. If a 25-mer comprises the 20-mer, the maximum potential identity is 20/25, which is 80%. If a 26-mer comprises the 20-mer, the maximum potential identity is 20/26, which is 77%. Therefore, the embodiments of oligonucleotides that are 23-26 nucleotides in length cannot meet the instant identity requirement with SEQ ID NO: 2.

Allowable Subject Matter

Claims 20 and 21 are allowed, because they are free of the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755. The examiner can normally be reached on Monday-Thursday 6:30 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amy H. Bowman/
Patent Examiner
Art Unit 1635